Reflections on the Practice of R&D: Balancing Academic Curiosity Analyzing Observations for a Lifetime with Patient-centricity and Market-driven Necessities to Move Fast

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What does this mean?

Reverse

Translation

Break through language barriers
Determinants of Success

Does size matter in R&D productivity? If not, what does?

Michael Ringel, Peter Tollman, Greg Hersch and Ulrik Schulze

NATURE REVIEWS | DRUG DISCOVERY V12, DEC 2013, 901

Integration of Various Scientific Pieces is NOT AN EASY TASK!
Implementation of QSP is a long and complex process. QSP cycles are defined by integration of experimental data and biological knowledge, generation of hypotheses & testing of those hypotheses with experiments.

Leil & Bertz 2015
Modelling Based on Simulated Concentrations in Liver

OATP1B1 c.521T>C associated with a 2.6% lower fractional LDL-C reduction per allele in <3000 patients treated with rosuvastatin daily (Chasman et al., 2012)!
The Challenges: Reference Point (systemic vs organ)

**Diagram:**
- Compound PK
- $X(t)$
- Effect compartment
- $X_e(t)$
- PD Basic Response

**Equation:**

$$AUC_{tissue} = \frac{AUC_{sys}}{CL_{in}} \cdot CL_{out}$$

M. Jamei · F. Bajot · S. Neuhoff · Z. Barter · J. Yang · A. Rostami-Hodjegan · K. Rowland-Yeo

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Figure 1. Proportion of 2013 and 2014 approvals without explicit dosing recommendations at the initial approval.
Why Has Model-Informed Precision Dosing Not Yet Become Common Clinical Reality? Lessons From the Past and a Roadmap for the Future

Renal elimination of drugs

- Active uptake via OAT1/3, OCT2 paired with efflux transporters MRP2/4, MATEs
- Proximal tubule cells also express drug metabolising enzymes
- Reabsorption - generally passive, active reabsorption via OAT4, PEPT1/2
Systematic evaluation of the CKD effect on CYPs

- CYP2D6-mediated clearance decreased in parallel with the severity of CKD
- No apparent relationship between the severity of CKD and CYP3A4/5-clearance

Effect of CYP1A2, CYP2C8, CYP2C9 and CYP2C19 – Poster Tan et al.
Yoshida Clin Pharmacol Ther 2016
Effect of CKD on OATP1B1

- Decrease in clearance in parallel with CKD severity

- Challenges:
  - Lack of binding data in RI subjects
  - Overlap between CYP2C8 and OATP1B1 model drugs

Poster Tan et al. - ITCW and ASCPT PT-020
Digoxin mechanistic kidney model verification

**Graphs A to F**

- **A** and **B**: Plasma concentration (µg/L) and Urinary excretion rate (µg/h) over time (h) from 0 to 144 hours.
- **C** and **D**: Same as **A** and **B**, but with a higher time range from 0 to 288 hours.
- **E** and **F**: Similar graphs as **A** and **B**, but with a different scale for plasma concentration.

**Legend**

- Purple circle: Plasma concentration
- Black line: Urinary excretion rate
Mechanistic digoxin kidney model: prediction of $\text{CL}_R$ in severe renal impairment

Additional mechanisms considered: i) ↓ transporter expression or ii) ↓ number of tubular cells

\[
\text{CL}_R \text{ ratio} = \frac{\text{CL}_R \text{ (renal impairment)}}{\text{CL}_R \text{ (healthy subjects)}}
\]

Change in GFR only (severe renal impairment; GFR = 15 – 30 mL/min)
Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

Draft

Objectives and Points to consider—EMA Workshop on extrapolation of efficacy and safety in medicine development across age groups

What are the challenges? Variable ontogeny (enzymes/transporters)
Relative Importance of Pathways: “Ratio of Ratios”!

Age Related Changes in Fractional Elimination Pathways for Drugs: Assessing the Impact of Variable Ontogeny on Metabolic Drug–Drug Interactions


Farzaneh Salem, PharmD¹, Trevor N. Johnson, PhD², Zoe E. Barter, PhD², J. Steven Leeder, PharmD, PhD³,⁴,⁵, and Amin Rostami-Hodjegan, PharmD, PhD, FCP¹,²

Relative Ontogeny =

Pathway A in Paediatrics
Pathway A in Adults
Pathway B in Paediatrics
Pathway B in Adults

Relative Importance of Pathways: "Ratio of Ratios"!
Ontogeny of Plasma Proteins, Albumin and Binding of Diazepam, Cyclosporine and Deltamethrin
Sethi; et al
Pediatric Research accepted article preview online 16 November 2015;

Absence of info on free local concentrations: Sensitivity???
An age-related trend in the magnitude of DDIs could not be established. However, the study highlighted the clear paucity of the data in children younger than 2 years. Care should be exercised when applying the knowledge of DDIs from adults to children younger than 2 years of age.
5.2.5. Special Populations

An interaction effect **may not be directly extrapolated** to specific subpopulations that have a markedly different contribution of the affected enzyme and/or transporter to the clearance of the investigational drug. Such subpopulations may include carriers of certain alleles…impaired renal function…and young paediatric patients (< 2 years)

……it may also be acceptable to use PBPK simulations to predict the interaction effect in the subpopulation if the simulation is qualified for this purpose. This includes an adequate prediction of the relative contribution of enzymes to *in vivo* clearance. Thus, the results of potent inhibition (or polymorphism) of the separate enzymes *in vivo* should be well predicted. ……**PBPK simulations may serve as a basis for treatment recommendations.** However, specific dose recommendations may need support by *in vivo* interaction data in the subpopulation.
True vs Apparent PD Differences in Paediatrics

Tyrosine hydroxylase (TH)

Rothmond et al., 2012
Combining the ‘bottom up’ and ‘top down’ approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data

Nikolaos Tsamandouras,¹ Amin Rostami-Hodjegan¹,² & Leon Aarons¹

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We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been.

George Wilhelm Merck
Physiologically Based Pharmacokinetics Joined With In Vitro–In Vivo Extrapolation of ADME: A Marriage Under the Arch of Systems Pharmacology

A Rostami-Hodjegan

Schematic Representation of Workflow

- Systems Data
- Trial Design
- Drug Data

PBPK-IVIVE Linked Models

Assessment of Covariates & Study Design using PK (PD) Simulated the Target Population

Associated IT Elements

Input Data:
- Population Library
- Compound File
- Project (Workspace)

Integrated Models
- Simulation Tool
- Simulation Environment

Output
- Raw Output Data
- Output Environment
- Data Analysis
“Your shoe fits the size of your foot, so why is your drug dose not tailored to your own personal characteristics in the same way? Why do drugs all come in one size fits all? OK may be only two sizes!”
Regulatory Framework

Medication Use in Pregnancy and the Pregnancy and Lactation Labeling Rule

L Sahin¹, SC Nallani² and MS Tassinari¹

8. USE IN SPECIAL POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

Pregnancy Registry
Risk Summary
Clinical Considerations
(Includes “Dose adjustments during pregnancy and the postpartum period”)
Data

Risk Summary
Clinical Considerations
Data

Pregnancy Testing
Contraception
Infertility

A brief outline of the re-formatted labeling: In each subsection, clinical pharmacology data can be included.

See draft guidance: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.¹

Figure 1  The pregnancy and lactation labeling final rule and changes to the prescription drug labeling.
3. Advancing Model-Informed Drug Development

To facilitate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources, herein referred to as “model-informed drug development” (MIDD) approaches, FDA will conduct the following activities during PDUFA VI:

a. FDA will develop its regulatory science and review expertise and capacity in MIDD approaches. This staff will support the highly-specialized evaluation of model-based strategies and development efforts.

b. FDA will convene a series of workshops to identify best practices for MIDD. Topics will include: (1) physiologically-based pharmacokinetic modeling; (2) design analysis and inferences from dose-exposure-response studies; (3) disease progression model development, including natural history and trial simulation; and (4) immunogenicity and correlates of protection for evaluating